Should phenotype of previous preterm birth influence management of women with short cervix in subsequent pregnancy? Comparison of vaginal progesterone and Arabin pessary

Can previous preterm birth classification influence treatment of short cervix in a subsequent pregnancy? Comparison of vaginal progesterone and Arabin pessary.

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Abstract

Objective

The aim of this study was to investigate whether the classification of a previous spontaneous preterm birth (sPTB) into; i) sPTB or ii) PPROM, impacts the efficacy of cervical pessary or vaginal progesterone in pregnant women with short cervix on transvaginal ultrasound.

Methods

Four European hospitals using pessary or vaginal progesterone as a primary PTB prevention treatment for asymptomatic high-risk singletons with a short cervix, provided retrospective cohort data. A log-rank test on Kaplan-Meier curves assessed the difference in performance of pessary and progesterone depending on history of sPTB or PPROM. A linear regression analysis evaluated significant predictors of gestational age at delivery.

Results

Between 2008-2015, 170 women were treated with pessary and 88 with vaginal progesterone. Rate of sPTB <34 weeks were 16% for 'pessary + sPTB history', 55% for pessary + PPROM history, 13% for 'progesterone + sPTB history' and 21% for 'progesterone + PPROM history'. Treatment with a pessary resulted in earlier delivery in women with previous PPROM than in any other subgroup; p=<0.0001 (p = 1.45e−09). Linear regression showed clear effect of PPROM history (p=7.773e-10), an interaction of PPROM with treatment (p = 0.0002590) and effect of CL (p = 0.0003763) on gestation at birth.

Conclusion

Cervical pessary may be a less efficacious treatment option for women with previous PPROM, however results require prospective validation before change in practice is recommended. Phenotype of previous preterm births may be an important risk predictor and treatment effect modifier; this information should be reported in future clinical trials.

Introduction

The presentation of preterm birth remains important for identifying the cause, estimating the risk of recurrence and implementing preventative strategies in subsequent pregnancies. A broad classification system of preterm birth based on presentation includes iatrogenic preterm birth, spontaneous preterm birth (sPTB) and preterm prelabor rupture of the membranes (PPROM) – each accounting for approximately one third of all preterm births.[1]

More recently preterm birth classifications use an increasingly complex conceptual framework based on severe maternal, fetal, and placental conditions causally associated with preterm birth.[2] Presently it is difficult to know how to apply this classification system to the management of subsequent pregnancy; many pregnancy observable characteristics fall across a minimum of two classifications and interventions for prevention remain limited. The only presentation for which there is effective intervention in singletons to prevent spontaneous preterm birth is a previous history of sPTB and/or a short cervix.[3,4]

There is increasing evidence from systems biology (the computational and mathematical modeling of complex biological systems) that sPTB(with intact membranes at labor, sPTB) and PPROM have distinct biological pathways.[5] An autoimmune/hormonal regulation axis may exist for sPTB, whilst pathways implicated in the etiology of PPROM include hematologic/coagulation function disorder, collagen metabolism, matrix degradation and local inflammation. Additionally, the dissimilarity of clinical risk factors for PPROM and sPTB suggest that there are different underlying pathophysiological pathways.[6]

It is therefore reasonable to hypothesize that treatments for short cervix may exert different biological and environmental interactions and effects resulting in different pregnancy outcomes. Although exact mechanisms of action remains to be established, the action of vaginal progesterone and pessary are likely to be different mechanisms of therapeutic effect. The pessary is a device which provides mechanical support and increases the uterocervical angle at the cervix[7] whereas vaginal progesterone has anti-

inflammatory properties and inhibits production of stimulatory prostaglandins (PG) and expression of contraction associated protein genes in the myometrium. [8]

We investigated the success of vaginal progesterone and Arabin pessary based on the classification of previous spontaneous preterm pregnancies. Our aim was to compare the outcomes following both treatments in women who had previously experienced only sPTB compared to PPROM.

Methods

We identified four hospitals one in Liverpool, UK (Liverpool Women's Hospital– LWH), two in Barcelona, Spain (Vall d'Hebron –VH; Hospital Clinic Barcelona – HCB) and one in Turin, Italy (Università degli Studi Torino – TOR) who have been using either cervical pessary (a CE-certified pessary; CE 0482 / EN ISO 13485: 2003 annex III of the council directive 93/42 EEC) or vaginal progesterone 200mg nocte as a primary treatment for preterm birth prevention between 2008 and 2015. We classified all women into two groups; a history of sPTB only ≤34 weeks or a history of PPROM ≤34 weeks. Classification was performed by preterm birth experts at each unit to classify these cases as correctly as possible. Any women who had pregnancies complicated with both sPTB and PPROM were included in the PPROM group. Our definition of PPROM for this study was a diagnosis of spontaneous rupture of the membranes at least 12 hours prior to delivery. We excluded all women with a history of a short cervix only (i.e. no history of preterm birth/PPROM), women treated prophylactically due to a history of sPTB or PPROM but no short cervix, cases where cervical length data were not available, multifetal pregnancies, congenital abnormalities diagnosed in the fetus and cases with cervical cerclage as a first line therapy. Short cervix was defined by individual hospital protocols but was either a single measurement of ≤25mm or less than 3rd centile for gestational age.[9] Ethical approval was obtained at each hospital for use of patient data to be analyzed retrospectively.

Our primary outcome was gestational age at delivery. For the primary analysis we excluded all women who had been additionally treated with a cervical cerclage or who had swapped treatment or added additional treatment based on a clinical perception

that the primary treatment was failing. A secondary analysis included all women based on an intention to treat principle.

Statistical Methods

Demographic data variables included in analysis were age, ethnicity, BMI, smoking, cervical surgery, number of term deliveries, number sPTB, number PPROM, GA earliest sPTB/PPROM and treatment for short cervix. IBM SPSS Statistics for Windows, Version 22.0. (Armonk, NY: IBM Corp) was used to calculate *P* values using one-way ANOVA, Kruskal Wallis, Mann-Whitney U test, chi squared test or Fishers exact test as appropriate. Subsequently demographics were compared between women who had previously experienced sPTB only or PPROM. A log-rank test on Kaplan-Meier curves was performed to assess the difference in performance of VP and AP depending on history of sPTB or PPROM, using the software package R (https://cran.r-project.org/) In order to establish which clinical characteristics are significant predictors of gestation at delivery and by what magnitude they contribute to this pregnancy outcome we have also performed a linear regression analysis using type of treatment, cervical length and phenotype of previous preterm birth as potential predictors.

Results

Data on 258 women with a history of PPROM or sPTB who had a subsequent treatment for short cervix with Arabin pessary or vaginal progesterone were obtained from four obstetric centers in Europe between 2008 and 2015 (Figure 1). Arabin pessary was the primary therapy in 170 women, 10 (6%) of whom required an additional therapy or change in treatment. Vaginal progesterone treatment was used in 88 cases and in 21 of them (24%) patients received an alternative or additive treatment following further cervical shortening. These 31 women with alternative or additive therapy were excluded from the primary analysis. Demographic data for the full cohort by centre and treatment group is included in supplementary table 1. The demographics for the remaining 227 women are shown by centre (table 1) and by treatment/history (table 2). Significant demographic differences between hospital

populations include tobacco use, cervical surgery and gestation at treatment with Turin centre screening until a later gestation than the other three hospitals (table 1), however there was no statistical significant difference in gestation at delivery by centre (p = 0.45). BMI was slightly lower in the 'PPROM + Progesterone' group with we felt that such a small difference, although statistically significant, would not be clinically important. Cervical surgery rates (24%) were also found to be higher in this group but this did not affect treatment performance measured by gestation at delivery. There was a significant increase in the number of women who had PPROM in their pregnancy if they had previously had PPROM compared to sPTB (32% versus 9%, P=<.001) (table 2). Overall women with a history of PPROM were more likely to deliver earlier than women with a history of sPTB (38 weeks versus 35 weeks, p = <.001).

Using a log rank test on Kaplan-Meier survival curves, a four-way comparison was performed to assess if there was any difference in duration of pregnancy between 4 distinct groups: i) previous PPROM treated with Arabin pessary; ii) previous sPTB-treated with Arabin pessary; iii) previous PPROM treated with vaginal progesterone; iv) previous sPTB treated with vaginal progesterone. Overall, the difference between 4 groups was highly significant (p<0.0001) due to much shorter gestation at delivery in women with previous PPROM treated with Arabin pessary. (Figure 2) When only women treated with progesterone were compared, there was no difference in the duration of pregnancy between women with previous PPROM and those with previous sPTB (p = 0.365). The results remained qualitatively unchanged when 31 women who received combination treatment were included (intention to treat analysis, data included in Supplementary Figure 1). The median gestational age for women on vaginal progesterone (n=21 total; n=10 prev PPROM) who had additive or changed treatment was 38 weeks (range 18-41wks) compared to 27 weeks (range 19weeks – 38weeks) in the Arabin group (n=10 total; n=6 prev PPROM).

We noted that the shortest cervical lengths at treatment were clustered in the Arabin + PPROM group, with the median cervical length at treatment lower in this group by 3 to 5mm (Table 2; p=0.021). As shorter cervical length is a known risk factor for PTB we

performed a linear regression analysis to determine if cervical length affected both the allocation of group and outcome. Our data confirmed that cervical length seems to be an independent predictor of gestation at birth (p=0.0003763), that is neither modified by nor modifying other factors. However, the strongest variables predicting earlier gestational age at delivery in our dataset were a history of PPROM (p=7.773e-10) and a combination of a history of PPROM and treatment (p = 0.0002590). Combining cervical length with treatment or PPROM history did not improve the prediction of gestational age at delivery.

Discussion

Analysis of data from this retrospective study have demonstrated that the previous observable characteristic of PPROM maybe an important predictor of the treatment success for short cervix in subsequent pregnancies. The Arabin pessary does not appear to have the same benefit in women who previously have experienced PPROM, compared to those with previous sPTB. Vaginal progesterone may, therefore, be a more efficacious treatment option for these women.

The pathophysiological mechanism behind this effect is not clear. One possible theory is that the Arabin pessary may exacerbate a dysbiotic vaginal microbial environment. *Kindinger et al.* have looked at the effect suture material has on the vaginal environment for a similar at risk population. They demonstrated that, compared to a braided suture, a monofilament material reduced the risk of preterm birth by an additional 11% and also reduced rates of nonviable births (<24 weeks or intrauterine death).[10] This causal effect was further supported by evidence that despite dysbiotic microbiomes being equal in prevalence prior to suture insertion, braided cerclage led to a shift towards dysbiosis in just 4 weeks after insertion. The Arabin pessary is a cone shaped silicone device that, once sited around a cervix, remains in the vagina until removal prior to labor. We hypothesize that similar effect could be involved here but found no published studies investigating an Arabin pessary's possible impact on surrounding vaginal microbiome. One study examining ring pessaries for pelvic organ prolapse in a non-pregnant population demonstrated that they could exacerbate

growth of pre-existing anaerobic bacteria.[11] The foreign body of the pessary could provide a surface for colonization, or alternatively many Arabin pessary users report a marked increase in watery discharge, which could affect vaginal microbial flora. In contrast, vaginal progesterone does not have any adverse impact on vaginal microbiota in pregnancy.[12]

The effect of different outcomes in different populations may, at least in part, account for the variation that we have seen in recent years in the mixed outcomes of clinical trials of Arabin pessary for a short cervix. The landmark paper that brought Arabin pessary into more frequent use as an alternative to vaginal pessary and cervical cerclage in current clinical practice was the PECEP trial published in 2012 which reported a significant reduction in spontaneous delivery before 34 weeks of gestation.[13] Mixed results have been reported in subsequent clinical trials of pessary for short cervix without satisfactory explanation.[14-16] As most studies collect limited data on the observable characteristics of previous preterm births or any other biomarkers, further individual patient data analyses are unlikely to provide better evidence of the importance of various classifications of preterm labour as potential modifiers of treatment success.

We acknowledge that our data are retrospective and therefore we cannot be certain that all classifications were assigned correctly. However, cases of sPTB and PPROM were reviewed by preterm birth experts at each unit to classify each case as correctly as possible. We would recommend the results of this study be validated in a separate population before advising a change in clinical practice. Our data is not randomized and therefore confounding as a cause of our results cannot be completely excluded.

Although women in each group had a comparable distribution of cervical lengths, but the median measurement was lowest in the Arabin + PPROM group at 17mm.However, a history of PPROM alone and PPROM interacting with treatment type were both independent predictors of gestational age at birth irrespective of cervical length when treatment was initiated. Whether in fact the pessary is exacerbating the risk of preterm birth in women with previous PPROM or alternatively

progesterone is modifying the risk from PPROM should be validated in future prospective studies.

We did not explore the reasons that 10% of women given Arabin and 24% of women commenced on progesterone were given additional treatment, this may reflect ongoing shortening of the cervix, lack of faith in the treatment by the clinician or the patient or physical discomfort with treatment. The concern for the analysis was that patients requiring a second treatment may be at higher risk of delivering and bias our results by removing them, particularly as there are a greater percentage of the progesterone group. Our intention to treat analysis (including all cases) revealed irrespective of women changing or adding treatments, women with a history of PPROM who receive an Arabin pessary as first line treatment remain at increased risk of delivering earlier than women receiving vaginal progesterone (supplementary figure 1; p = 3e-09).

Regrettably, we were unable to test in our data set whether the phenotype of previous preterm birth is also relevant for cervical cerclage. This may be potentially very important given that significant number of UK preterm birth prevention clinics still use cervical cerclage as a first line treatment for short cervix[17]

The data from this study have fundamental implications for ongoing clinical trials into preterm birth treatments. We argue that data collection should take into account the observable characteristics of the previous preterm birth to allow sub classification of results based on previous history. In depth classifications have been published,[2] but as a minimum trying to identify subgroups of sPTB and PPROM would be recommended. The authors acknowledge that the classification of PPROM can be particularly challenging given the subjectivity surrounding “the beginning of labor”, inability to access previous pregnancy details and poor note keeping. Ideally, the phenotyping should also include other key features of the index pregnancy in addition to cervical length, including vaginal microbiome, quantitative fetal fibronectin and blood samples for biomarker testing (genomics, transcriptomics, proteomics etc.). Clearly, there are important implications on the design and size of future clinical trials if we expect to

test the effectiveness of ever smaller groups of patients, but better phenotyping would, as a minimum, encourage increased data sharing and much more informative and clinically useful individual patient data meta-analysis.

Conclusion

Arabin pessary may not be as effective in women who have previously experienced PPROM, compared to women with a history of sPTB. This differential effect is not seen with vaginal progesterone that may, therefore, be a better treatment choice for women with a history of PPROM and short cervix in pregnancy. This data suggests that it may be possible to stratify treatments for short cervix. We recommend data on previous pregnancy characteristics should be routinely collected as part of clinical trials of preterm birth prevention to evaluate this effect in other populations.

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Conflict of Interest/ Disclosure Statement

A.C. and Z.A. performed a feasibility randomized clinical trial of arabin pessary, vaginal progesterone and cervical cerclage in 2016. The vaginal progesterone was supplied by Besins Healthcare at no cost. No funding or stock was received for this study. The remaining authors report no conflict of interest.

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Table 1. Characteristics of women with previous sPTB/PPROM and short cervix by centre.

	Liverpool Women's LWH (n=77)	Barcelona Vall d'Hebron VH (n=98)	Hospital Clinic Barcelona HCB (n=20)	Turin TUR (n=32)	P value
Age, yrs*	31 (5)	31 (5)	33 (5)	32 (4)	.514†
BMI*	25 (5)	26 (3)	23 (5)	25 (4)	.100†
Ethnicity (% within centre)					
Caucasian	66 (85.7)	57(58.2)	18 (90)	28 (88)	
Black	9 (11.7)	8 (8.2)	0	3 (9.4)	
Asian	1 (1.3)	10 (10.2)	0	0	N/R
Indian	1 (1.3)	0 (0)	0 (0)	0 (0)	
Hispanic	0	23 (23.5)	2(10	0 (0)	
Tobacco Use, n (%)	26 (34)	21 (21)	4(20)	3 (9)	**.039‡**
Cervical surgery, (%)	15 (19)	1 (1)	2 (10)	3 (9.4)	**<.001‡**
Gestation at Rx, weeks§	21 (14-28)	22 (19-24)	23 (9-29)	25 (15-32)	**.001¶**
Cervical Length at Rx (mm)§	20 (3-29)	20 (5-25)	21 (9-24)	20 (0-27)	.401¶
Arabin pessary	38	98	0	24	N/R
Vaginal progesterone	39	0	20	8	N/R

*Mean (SD) †Oneway ANOVA ‡Chi squared §Median (range) ¶Kruskal Wallis test

Table 2. Demographics and pregnancy outcomes for all 227 women included in primary analysis

	Pessary (n= 160)		Progesterone (n=67)		P value
Previous History	**sPTB (n=129)**	**PPROM (n=31)**	**sPTB (n=38)**	**PPROM (n=29)**	
Demographic Data					
Age, yrs*	31 (5)	32 (5)	31 (6)	32 (4)	.745†
BMI*	25 (4)	25 (4)	25 (4)	23 (5)	**.043**†
Ethnicity (%)					
Caucasian	92 (71)	17 (55)	33 (87)	27 (93)	N/R
Black	11 (9)	5 (16)	3 (8)	1 (3)	
Asian	4 (3)	6 (19)	0	1 (3)	
Indian	1 (1)	0	0	0	
Hispanic	21 (16)	3 (10)	2 (5)	0	
Tobacco Use, n (%)	31 (24)	5 (16)	10 (26)	8 (28)	.712‡
Cervical surgery, n (%)	9 (7)	2 (7)	4 (11)	7 (24)	**.038**‡
Gestation at Rx, wks §	22 (16-32)	22 (16-30)	22 (14-29)	22 (16-30)	.941¶
Cervical Length at Rx (mm) §	20 (3-29)	17 (4-27)	21 (6-27)	22 (0-26)	**.021**¶
Pregnancy Outcomes					
Gestation at Delivery, w§	38 (22-41)	29 (21-40)	38 (27-41)	37 (23-41)	**<.001**¶
PPROM, n (%)	11 (9)	10 (32)	4 (11)	9 (31)	**<.001‡**
PTB < 34 weeks, n (%)	21 (16)	17 (55)	5 (13)	6 (21)	**<.001‡**
CS, n (%)	20 (16)	5 (16)	5 (13)	7 (24)	.650‡

*Mean (SD) †Oneway ANOVA ‡Chi squared §Median (range) ¶Kruskal Wallis test

Figure Legends

Figure 1. Flow diagram of cases included.

Figure 2. Survival curves demonstrating preterm birth probabilities by obstetric history and treatment group in primary analysis (n=227)

Supplementary Table 1 Demographics and pregnancy outcomes for all 258 women included in intention to treat analysis

Supplementary Figure 1 Survival curves demonstrating preterm birth probabilities by obstetric history and treatment group (n=258)